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ORIGINAL ARTICLE

Direct-acting antivirals in women of reproductive age infected with hepatitis C virus

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Abstract

Eliminating hepatitis C virus (HCV) infection in the population of women of reproductive age is important not only for the health of women themselves but also for the health of newborns. This study aimed to evaluate the implementation of this goal by analysing the effectiveness of contemporary therapy in a large cohort from everyday clinical practice along with identifying factors reducing therapeutic success. The analysed population consisted of 7861 patients, including 3388 women aged 15–49, treated in 2015–2022 in 26 hepatology centres. Data were collected retrospectively using a nationwide EpiTer-2 database. Females were significantly less often infected with HCV genotype 3 compared to males (11.2% vs. 15.7%) and less frequently showed comorbidities (40.5% vs. 44.2%) and comedications (37.2% vs. 45.2%). Hepatocellular carcinoma, liver transplantation, HIV and HBV coinfections were reported significantly less frequently in women. Regardless of the treatment type, females significantly more often reached sustained virologic response (98.8%) compared to males (96.8%). Regardless of gender, genotype 3 and cirrhosis were independent factors increasing the risk of treatment failure. Women more commonly reported adverse events, but death occurred significantly more frequently in men (0.3% vs. 0.1%), usually related to underlying advanced liver disease. We have demonstrated excellent effectiveness and safety profiles for treating HCV infection in women. This gives hope for the micro-elimination of HCV infections in women, translating into a reduced risk of severe disease in both women and their children.

KEYWORDS
direct-acting antivirals, hepatitis C virus, reproductive, women

Abbreviations: BMS, bristol myers squibb; GSK, Glaxosmithkline.

For affiliations refer to page 8.

1 | INTRODUCTION

In recent years, an increase in the number of hepatitis C virus (HCV) infections has been observed among young women, in particular due to the intravenous use of psychoactive substances, piercing procedures and tattooing.[1,2] According to the Centers for Disease Control and Prevention (CDC) (USA), the national rate of HCV infection among women giving birth in the U.S. increased by more than 400% from 0.8 per 1000 deliveries in 2000 to 4.1 in 2015. Rates were much higher (87.4 and 216.9/1000 deliveries, respectively) among women with a history of opioid use disorder, but an increase from 0.7 to 2.6/1000 deliveries was also observed in women who did not use opioids in the past.[1] In Poland, the prevalence of anti-HCV among pregnant women in 2004–2014 period was 0.8% and was similar to the prevalence in other Central European countries (1%).[3,4]

Detection of infection during pregnancy enables treating the woman soon after delivery and diagnosing possible HCV infection in her child. It has been shown that in individuals vertically infected with HCV, liver cirrhosis develops at a younger age and more often than in those infected later in life.[5] However, it is strongly advocated that testing before pregnancy to apply therapy and eliminate HCV infection before conception to protect both the mother and the child.

It is now recommended that young women of childbearing age be tested for HCV infection, as they are a special risk group for HCV infection and should undergo universal screening. This is because HCV infection is an important cause of fertility disorders, including adverse pregnancy outcomes such as stillbirth, miscarriage, fewer live births and gestational diabetes.[6–8]

Young women are at risk of HCV infection both due to risky behaviours (e.g. drug use, sexual behaviour, tattoos) and typically female professions associated with increased exposure to infection (e.g. health care and sex workers).[9–11] The natural history of HCV infection in women is characterized by a higher rate of spontaneous elimination of HCV viremia compared to men and a slower progression to cirrhosis and HCC in the premenopausal period.[12] These percentages level off and even reverse in postmenopausal women when the frequency of HCV infections and progression to unfavourable clinical consequences is significantly higher in women.[13] Early detection of HCV infection provides the opportunity for rapid qualification for treatment, which guarantees complete elimination of the infection and, consequently, inhibition of liver disease progression to liver cirrhosis and hepatocellular carcinoma (HCC), possible fertility disorders and finally reduces the risk of vertical transmission of HCV to newborns.

Additionally, women are more likely to achieve a sustained virological response after antiviral treatment.[14] It may be, at least partially, a result of hormonal action since 17-beta-estradiol has been shown to disrupt the HCV life cycle through intracellular receptor signalling, inhibiting virus production and may also inhibit HCC development as shown in vitro and in vivo, though clinical trials have shown inconsistent results in this regard.[15–20] Women's sex hormones, in particular oestrogen, are also partially responsible for the lower aggressiveness of liver cancer, as well as a better response to treatment, a lower rate of recurrence and an overall better prognosis.[20,21]

Since, in light of available knowledge, the elimination of HCV infection in the population of women of reproductive age is of significant health and epidemiological importance, our analysis set the aim of assessing the realization of this goal by evaluating the effectiveness of DAA therapy in a large cohort from daily clinical practice with the identification of factors that reduce the chance of therapeutic success.

2 | MATERIALS AND METHODS

2.1 | Study population

The analysed population included 7861 patients, 3388 women and 4473 men with chronic hepatitis C who, at the time of starting antiviral treatment, were in the age range of 15–49 years, which according to the World Health Organization (WHO), the reproductive age for women, while we considered men of this age as a comparison group (Figure 1).[22]

Patients were treated between 2015 and 2022 at 26 adult and paediatric hepatology centres located in Poland, and the therapy was reimbursed by the National Health Fund (NHF). The type of regimen was selected by the treating physician, depending on the requirements of the drug program, Summary of Product Characteristics (SmPC) and the recommendations of the Polish Group of Experts for HCV (PGE HCV) in effect at the time.[23–28] Patients or their legal guardians have given informed consent for treatment and processing of personal data in accordance with the requirements of the drug programme and national regulations.

2.2 | Data collection

Data collection was performed retrospectively using a nationwide database that is part of the EpiTer-2 multicentre project. We performed an overall analysis based on patient sex using demographic and clinical characteristics such as age, body mass index (BMI), HCV genotype, comorbidities, hepatitis B virus (HBV) and human immunodeficiency virus (HIV) co-infection. Treatment characteristics and safety were also considered. We analysed sustained virologic response (SVR) at 12 weeks after the end of treatment (EOT) according to HCV genotype (GT3 versus nonGT3), liver fibrosis (F0–F3 vs. F4) and type of treatment regimen (pangenotypic versus genotype-specific).

2.3 | Assessment of liver disease severity

Using transient elastography (TE), we assessed the advancement of liver disease corresponding to the degree of liver fibrosis

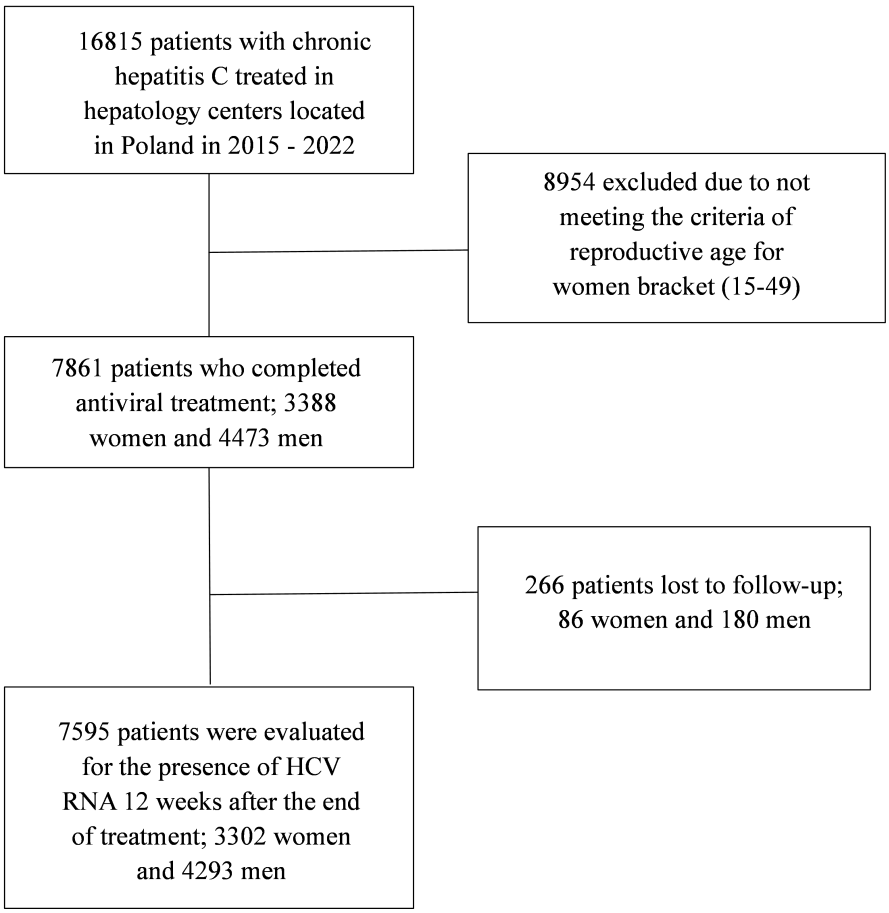

FIGURE 1 Overall flowchart of the design of the present study.

defined as F0–F4 according to the METAVIR score. The values in kilopascals included in the EASL recommendations were used for conversion.[29] The F4 value was interpreted as cirrhosis. Before initiating treatment, the treating physician assessed patients for the presence of HCC (hepatocellular carcinoma) and a history of liver transplantation. Decompensation of liver function was assessed at the start of treatment using the Child-Pugh scale, and information on whether it had ever occurred in the past was collected through medical history.

2.4 | Assessment of treatment effectiveness and safety

The SVR was used as an efficacy endpoint. It was defined as undetectable HCV RNA at least 12 weeks after the EOT. An undetectable HCV RNA at this time point signified a response to treatment, while a detectable viral load categorised the patient as virologically unresponsive. Lost-to-follow-up patients were considered non-virologic failures due to a lack of HCV RNA evaluation.

Safety data included modification or discontinuation of therapy, occurrence of adverse events (AEs), severe AEs and deaths. Data were collected during treatment and for 12 weeks after EOT. AEs of particular importance, such as gastrointestinal bleeding, ascites and encephalopathy, were intended to be monitored only in patients with cirrhosis.

2.5 | Ethics

Patients were treated with registered drugs according to the requirements of the drug programme and PGE HCV recommendations.[23–28] No experimental drugs were used. Patient data was collected and analysed by the applicable principles of personal data protection. Due to the observational, non-interventional nature of the study with the use of marketed drugs, according to the local law in force at the time of the study (Pharmaceutical Law of September 6, 2001, Article 37al), the consent of the ethics committee was not required.

2.6 | Statistical analysis

Continuous data were presented as a median and interquartile range and minimum and maximum values for some variables. The significance of the difference was assessed with the Mann–Whitney test because the data did not meet the Gaussian distribution; it was checked with the Shapiro–Wilk test. Categorical data were described as numbers and percentages. For nominal variables, group

comparison was performed using the χ^2 test. A stepwise multiple logistic regression model was used to understand which variables were independently associated with virological failure 12 weeks post-treatment in women and men. The variables for this model were selected based on the results of univariate analyses. All patients who initiated the treatment were included in the intent-to-treat (ITT) analysis, while only those who completed 12 weeks post-treatment follow-up with HCV RNA evaluation were appraised in the per-protocol (PP) analysis. A p-value less than .05 was considered significant. Statistical analyses were performed using Statistica v. 13 (StatSoft, Tulsa, OK, United States) and GraphPad Prism 5.1 (GraphPad Software, Inc., La Jolla, CA).

3 | RESULTS

3.1 | Patients' baseline characteristics

In the studied population of women and men between 15 and 49 years of age, the median (IQR) of BMI was significantly higher in men compared to women (25.93 [23.63–28.65] vs. 23.44 [21.09–26.64], respectively) (Table 1).

Women were significantly less often infected with genotype 3 (11.2%) compared to the male part of the studied population (15.7%). Overall, the presence of comorbidities was significantly more common in men (44.2% vs. 40.5%, $p = .001$, respectively), with hypertension and diabetes being the two most frequent in both groups. With the higher multimorbidity in men, usage of medications other than antivirals was higher in that group (45.2% vs. 37.2%, $p < .001$) (Table 1). Both hepatocellular cancer (HCC) and non-HCC tumours were reported less frequently in women; however, a significant difference was found only for HCC (0.5% vs. 0.1%, $p = .001$). HIV and HBV coinfections were diagnosed more commonly in men, with HIV present in nearly 14% of them compared to nearly 6% of the female population ($p < .001$). Men were also significantly more likely to have a history of liver transplantation (0.6% vs. 0.3%, $p = .02$).

3.2 | Treatment characteristics and effectiveness

Previous therapy was reported in 13.5% of women, and while men were significantly more often treatment-experienced (17.4%, $p < .001$), in both groups, regimens were mostly IFN-based. IFN-free therapies were chosen nearly three times more often for men than women (17.3% vs. 5.5%, respectively) (Table 1).

Current treatment regimens were evenly distributed, though there was a slight predominance of genotype-specific regimens used in women (55.4%), while pangenotypic ones were chosen more readily for men (50.5%; Table 1).

Regardless of the treatment type, both in ITT and PP analysis, women significantly more often reached virological clearance 12 weeks after the EOT than men (Figure 2).

The trend reflected the general analysis in which SVR in PP analysis was achieved by 98.8% of women and 96.8% of men (Figure 2). Only 86 women were considered lost-to-follow-up (LTFU), while the number of men was more than double. A stepwise multiple logistic regression was built using independent variables, which revealed significant differences in univariate analyses, that is, HCV genotype 3, presence of cirrhosis, presence of comorbidities such as autoimmune diseases, HBV and HIV coinfection and type of treatment used. Regardless of sex, GT3 was an independent factor in increasing the risk of virological failure 12 weeks post-treatment (Table 1, Figure 3). Similarly, F4 fibrosis, which presents more than twice as often in men as in women, was an independent factor negatively influencing virological clearance (Table 1, Figure 3). Moreover, men infected with GT3 more often discontinued therapy (1.0% vs. 0.3%) and presented with cirrhosis compared to women (26.6% vs. 13.6%, $p < .001$). Regardless of the type of regimen used, genotype-specific and pangenotypic, subpopulations according to genotype, GT3 and non-GT3 and degree of liver fibrosis, F0–F3 and F4, as well as the type of analysis, ITT and PP, women were significantly more likely to achieve SVR compared to men (Figure 2).

Assessment of behavioural risk factors showed that 0.6% of women and 1.9% of men reported addiction to drugs, and the difference was statistically significant. Methadone substitution therapy was utilised four times more often in men (1.6%) than in women (0.4%), with a p-value $< .00001$. Patients addicted to alcohol were significantly more often male and represented 4.4% of all patients lost to follow-up. Addiction to drugs and methadone treatment were noted in less than 2% of patients who missed assessment 12 weeks after EOT, while infection with GT3 was present in more than one-fourth of those considered lost to follow-up (Table 2). SVR was impacted only in the case of alcohol addiction, with 86.7% of patients reaching virological clearance in PP the analysis. All other groups noted SVR over 95% in PP analysis (data not shown).

3.3 | Treatment's safety

In the majority of patients, treatment was carried out according to schedule (98.5% women, 98.1% men), and the chance of severe adverse event (SAE) was low regardless of sex, and none was a direct result of antiviral treatment (Table 3). Women more commonly reported the presence of adverse events (AEs), with the two most frequent being weakness/fatigue (6.9% vs. 5.5%, $p = .01$) and headache (4.4% vs. 2.4%, $p < .001$). AEs of special interest were assessed only in those with liver cirrhosis, and none appeared significantly more often in either sex (Table 3). The death occurred more commonly in men (0.3% vs. 0.1%, $p = .03$), although none was assessed by the treating physician as related to antiviral therapy; in the majority of cases, it was the result of underlying advanced liver disease (Table 3).

TABLE 1 Baseline characteristics of patients aged 15–49 years included in the present study ($n = 7861$).

Parameter	Women ($n = 3388$)	Men ($n = 4473$)	p-Value
Age [years] median (IQR)	38 (32–43)	39 (34–43)	<.001
BMI median (IQR), [min-max]	23.44 (21.09–26.64), [13.2–57.44], $n = 3334$	25.93 (23.63–28.65), [14.57–52.47], $n = 4385$	<.001
GT, n(%)	n=3387	$n = 4473$	
nonGT3	3008 (88.8)	3771 (84.3)	<.001
GT3	380 (11.2)	702 (15.7)	
Fibrosis (METAVIR score), n (%)	$n = 3357$	$n = 4422$	
F4	253 (7.5)	818 (18.5)	
Comorbidities, n (%)			
Any comorbidity	1372 (40.5)	1976 (44.2)	.001
Hypertension	299 (8.8)	588 (13.2)	<.001
Diabetes	92 (2.7)	226 (5.1)	<.001
Renal disease	91 (2.7)	115 (2.6)	.75
Autoimmune diseases	108 (3.2)	39 (0.9)	<.001
Non-HCC tumours	30 (0.9)	35 (0.8)	.62
Concomitant medications, n (%)	1261 (37.2)	2026 (45.3)	<.001
History of HCC, n (%)	3 (0.1)	23 (0.5)	.001
History of liver transplantation, n (%)	9 (0.3)	28 (0.6)	.02
HIV coinfection, n (%)	189 (5.6)	611 (13.7)	<.001
HBV coinfection, n (%)	400 (11.8)	622 (13.9)	.006
History of previous therapy, n (%)			
Treatment-naïve	2932 (86.5)	3696 (82.6)	<.001
Treatment-experienced	456 (13.5)	777 (17.4)	
Previous regimen in patients with treatment failure, n (%)	$n = 456$	$N = 777$	
IFN-based	431 (94.5)	643 (82.8)	<.001
IFN-free	25 (5.5)	134 (17.3)	
Current treatment regimen, n (%)			
Genotype-specific	1876 (55.4)	2213 (49.5)	<.001
Pangenotypic	1512 (44.6)	2260 (50.5)	

Abbreviations: GT, genotype; HBV, hepatitis B virus; HCC; hepatocellular carcinoma; HIV, human immunodeficiency virus, IFN; interferon.

4 | DISCUSSION

According to the WHO, biologically, women between the ages of 15 and 49 are of reproductive age, even though in most countries, including Poland, the legal age of consent begins at 18.[20]

It is estimated that women of reproductive age 15–49 years, representing one-fourth of the world's population, constitute approximately 21% of all HCV-infected people.[30] However, the scale of the HCV problem related to this specific population is more significant due to the risk of mother-to-child transmission (MTCT).[31] Diagnosing the infection before procreation makes it possible to start antiviral treatment, which prevents MTCT, thus breaking the chain of infection, but also reduces the risk of pregnancy complications with a possible link to HCV infection, including cholestasis or gestational diabetes.[30–32] Due to this risk, scientific societies recommend universal screening for HCV infection in all pregnant women.[28,29,33] In Europe, based on data from 2005 to 2015, the prevalence of HCV in pregnant women ranges from 0.1% in Slovenia to 0.9% in Norway, with an estimated MTCT rate of 5.8%, reaching 10.8% in women reporting HIV co-infection.[34,35] Poland introduced the universal screening of pregnant women in 2018, and it is becoming a standard worldwide, with countries such as Canada reporting nearly four times more HCV-infected women diagnosed with universal screening (47.6%) compared to risk-based testing (12.5%).[36] It highlights that a group of undiagnosed women of reproductive age awaiting diagnosis and treatment is numerous. Pregnancy for females with

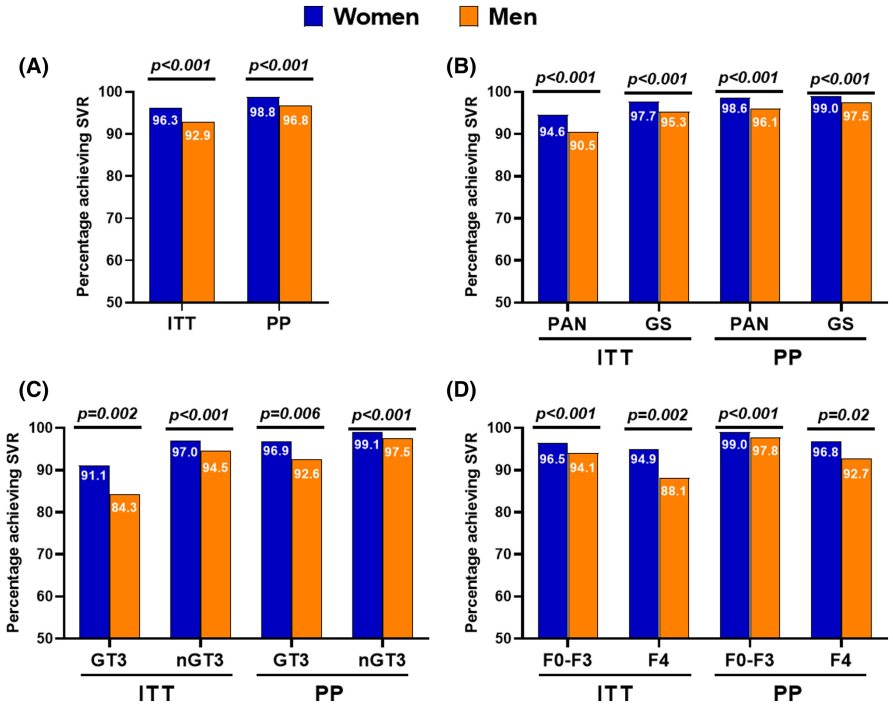

FIGURE 2 Comparison of sustained virologic response (SVR) between women and man in intent-to-treat (ITT) and per protocol analysis (PP) in (A) the studied cohort, (B) in relation to therapy type, pangenotypic (PAN) or genotype-specific (GS), (C) in relation to HCV genotype, non-genotype 3 (nGT3) or genotype 3 (GT3) and (D) in relation to the advancement of the liver disease referred to as non-cirrhotic (F0–F3) or cirrhotic (F4).

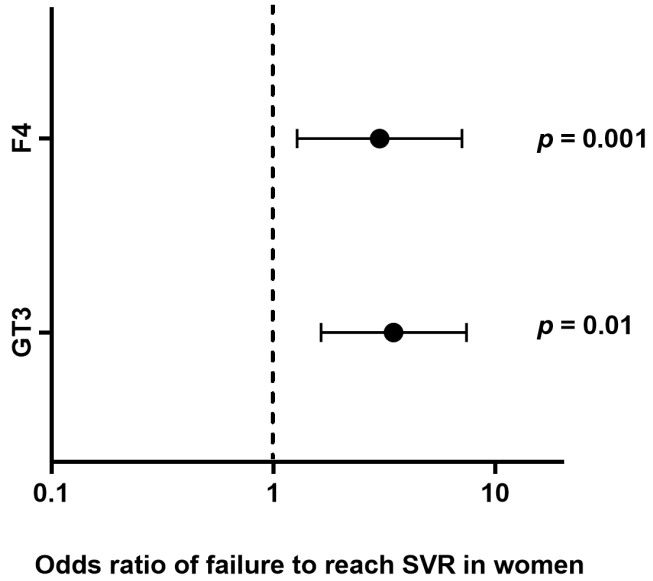

FIGURE 3 Forest plot of odds ratio (OR, 95% CI, *p*-value) from stepwise multiple logistic regression showing factors independently increasing the risk of virological failure 12 weeks post-treatment in females.

risk factors such as drug or alcohol addiction is often the only prolonged contact with healthcare, and it gives us ample opportunity for not only diagnosis but education and planning future treatment.

Women with HCV infection detected during pregnancy should be linked to care and treated with antivirals following pregnancy.[33] Since data on the safety of DAA treatment during pregnancy are very limited and are based on single reports regarding only genotype-specific regimens, it is recommended to initiate the treatment after delivery.[28,29,33,37–40] Recent interim report from phase 4, open-label, single-arm STORC study assessing the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) regimen administered after 20 weeks' gestation noted that all women reached virological clearance 12 weeks after treatment completion and none of the infants had detectable HCV RNA. The data provides reassurance that treatment with DAA will be recommended for pregnant women in the future.[41] However, currently, the guidelines of scientific societies recommend antiviral therapy in women of reproductive age before considering pregnancy.[23,29]

In reviewing phase III clinical trials that analysed the use of DAA in different HCV-infected populations, we found no specific data comparing group characteristics, course and treatment effect by sex, reporting only a higher rate of SVR12 in women compared to men. Only recently did Zhou et al. publish an analysis comparing DAA regimens by sex in patients infected with GT1 or GT3, based on data from 40 phase 3 clinical trials. They found that regardless of HCV genotype, women were more likely to achieve SVR.[42] This trend can also be seen in real-world studies and has been attributed to several factors, such as lower adherence and a higher prevalence of risk factors for failure in men.[43] Still, there is a gap regarding the detailed comparison of group characteristics, safety and effectiveness of treatment between women of childbearing age and men of the corresponding age. To fill this knowledge gap, we conducted our study in a large RWE cohort of several 1000 patients using retrospective data.

In our analysis, the larger group consisted of men, which may be due to the documented, significantly more frequent spontaneous elimination of HCV in women.[12] We confirmed that the population of women of childbearing age responds to DAA treatment at a very high rate of up to 99%, regardless of the type of regimen, genotype-specific or pangenotypic, so covering them with antiviral therapy is

TABLE 2 The frequency of addictions in women and men included in the studied group and in the subgroup that was lost to the follow-up (LFTU).

Parameter	Entire group ($n=7861$)		*p*-Value
	Women, $n=3388$	Men, $n=4473$	
Addiction to drugs, *n* (%)	19 (0.6)	85 (1.9)	<.00001
Methadone substitution therapy, *n* (%)	15 (0.4)	70 (1.6)	<.00001
Addiction to alcohol, *n* (%)	15 (0.4)	68 (1.5)	<.00001
Mixed addiction (drugs and alcohol), *n* (%)	4 (0.1)	22 (0.5)	.005
Parameter	**LTFU ($n=266$)**		***p*-Value**
	Women, $n=86$	**Men, $n=180$**	
Addiction to drugs, *n* (%)	1 (1.2)	3 (1.7)	1.0
Methadone substitution therapy, *n* (%)	1 (1.2)	2 (1.1)	1.0
Addiction to alcohol, *n* (%)	0 (0)	8 (4.4)	.05
Mixed addiction (drugs and alcohol), *n* (%)	0 (0)	1 (0.6)	1.0
GT3, *n* (%)	23 (26.7)	63 (35.0)	.18
F4, *n* (%)	5 (5.8)	40 (22.2)	.0008

Abbreviations: GT, genotype.

TABLE 3 Safety of an antiviral therapy in women and men aged 15–49 years included in the present study ($n=7861$).

Parameter	Women, $n=3388$	Men, $n=4473$	*p*-Value
Treatment course, *n* (%)	$n=3384$	$n=4466$	
According to schedule	3338 (98.5)	4389 (98.1)	.17
Therapy modification	22 (0.7)	41 (0.9)	.19
Therapy discontinuation	24 (0.7)	36 (0.8)	.63
Patients with at least one AE, *n* (%)	668 (19.7)	739 (16.5)	.00025
Severe adverse events, *n* (%)	11 (0.3)	20 (0.5)	.4
Most common AEs (≥2%), *n* (%)			
Weakness/fatigue	233 (6.9)	245 (5.5)	.01
Headache	150 (4.4)	107 (2.4)	<.001
AEs of special interest (cirrhotics), *n* (%)	$n=253$	$n=818$	
Ascites	9 (3.6)	18 (2.2)	.23
Hepatic encephalopathy	4 (1.6)	11 (1.3)	.78
Gastrointestinal bleeding	1 (0.4)	7 (0.9)	.46
Death, *n* (%)	2 (0.1)	12 (0.3)	.03

Abbreviations: AE; adverse event.

associated with a tremendous chance of success. These results are consistent with the effects of treatment for women, both in clinical trials and in RWE populations.[44–46] Importantly, we documented a significantly higher SVR rate among women than men of the same age. In multivariate analysis, liver cirrhosis and GT3 infection turned out to be negative predictors of response to DAA treatment in both sexes, and this conclusion from our study confirms the findings of other researchers, both from clinical trials and RWE studies.[47] However, despite GT3 infection and the presence of cirrhosis, in the current study, women of reproductive age were still more likely to achieve virological clearance than men, with a treatment response of 97% compared with 93% in men for both cirrhosis and GT3 infections. It is worth noting that in our research, both GT3 HCV infection and liver cirrhosis were diagnosed significantly more often in men, which is in line with the findings from other RWE studies.[48] The lower severity of liver disease is thought to be due to the protective effect of female sex hormones, which inhibit the activation of hepatic stellate cells and thus have an antifibrogenic role. This positive effect of oestrogens, responsible for differences in the severity of liver fibrosis in both sexes, wanes in the postmenopausal period.[13] A positive correlation between high testosterone levels and an increased risk of advanced liver fibrosis has also been documented.[49] The fact that total testosterone levels are significantly higher in menopausal women than in childbearing women is another argument for diagnosing and treating hepatitis C at reproductive age.[20]

Another difference between the treated patient populations recognised in our analysis was the significantly higher proportion of men with a history of previous therapy failure compared to women. Most of the treatment-experienced were treated with IFN-based regimens, to which, in the under-50 age group, men also responded worse than women, so a higher percentage of them required antiviral retherapy.[50]

In our analysis, women of childbearing age were significantly less burdened by comorbidities than men (40% vs. 44%) and were significantly less likely to require comedications (37% vs. 45%). In this regard, it is difficult for us to compare our results with other studies because, to the best of our knowledge, no research comparing patients at age below 50 years treated for HCV by sex has yet been published, while data on the population prevalence of comorbidities in this age group are disparate.[51]

Our analysis documented not only the excellent effectiveness of the therapy but also a very good safety profile. And although women were significantly more likely than men to report adverse events during therapy and the follow-up period, mainly weakness, fatigue and headache, this did not affect the course of treatment; the vast majority of patients completed therapy as planned. Those findings align with results reported by Zhou et al.,[42] where even though more females reported adverse events compared to males, the discontinuation rates remained low and similar between the two groups.

Looking at the data regarding drug and alcohol overuse among patients included in the database, only 0.6% of women and 1.9% of men were addicted to illicit substances, and 69.2% of them were treated with methadone substitution therapy. All the patients completed the full course of treatment, and SVR for both groups was over 95% in the PP analysis. Alcohol addiction proved to be a more challenging factor, with 8 (9.6%) patients lost to follow-up and 10 (12%) with virological failure. According to Poland's drug report from 2019, there are 14,664 high-risk opioid users, with 2685 patients on substitution treatment with methadone. While drug overuse is concentrated among young adults aged 15–34 years, they mostly use recreational cannabis, and only 3.7% of them are females. There is also a strong predominance of men among those entering specialised drug treatment in Poland, regardless of the drug used.[52] According to the World Drug Report by the United Nations Office on Drugs and Crime, men are five times more likely to reach for intravenously injected drugs than women, and among opioid users, they constitute 75% of the population; these disparities stay in line with our results.[53]

Our study has several limitations, of which we are aware. The retrospective nature of the research raises the risk of entry errors, missing data, possible bias and underestimation of the frequency of adverse events. Data on contraceptive methods was not gathered, which can be considered a major weakness of the study. However, each time there was a possible drug–drug interaction, the method of birth control was changed, and the treatment was initiated after the switch. Information on risk factors was limited to drug and alcohol addiction and substitution therapy with methadone. Moreover, phylogenetic analysis was not conducted, and the risk for reinfection was not assessed. However, the strongest point of our study was the assessment of a large, real-world population from many hepatology centres treating patients according to the same rules and recommendations, which means that the results obtained can be generalised.

5 | CONCLUSIONS

In a large, real-world population of HCV-infected women of reproductive age, we documented a good safety profile and excellent 99% effectiveness of DAA therapy, significantly higher compared to men in the same age group. The presence of independent negative predictors of virological response, GT3 infection and liver cirrhosis reduced the chances of effective therapy to 97%. Promising results of antiviral therapy provide hope for the microelimination of HCV infection in this population, which translates not only into reducing the health consequences of the infection but also preventing vertical transmission, which eliminates the risk of developing a severe disease not only in the woman but also in her child.

AUTHOR CONTRIBUTION

Conceptualization, Krystyna Dobrowolska, Małgorzata Pawłowska, Dorota Zarębska-Michaluk, Robert Flisiak; Data curation, Krystyna Dobrowolska; Formal analysis, Krystyna Dobrowolska and Piotr Rzymski; Funding acquisition, Robert Flisiak; Investigation, Krystyna Dobrowolska; Methodology, Krystyna Dobrowolska, Małgorzata Pawłowska, Dorota Zarębska-Michaluk, Piotr Rzymski, Robert Flisiak; Project administration, Robert Flisiak; Resources, Robert Flisiak; Supervision, Robert Flisiak; Validation, Robert Flisiak; Writing – original draft, Krystyna Dobrowolska, Małgorzata Pawłowska, Dorota Zarębska-Michaluk, Robert Flisiak; Writing – review & editing, Ewa Janczewska, Magdalena Tudrujek-Zdunek, Hanna Berak, Włodzimierz Mazur, Jakub Klapaczyński, Beata Lorenc, Justyna Janocha-Litwin, Anna Parfieniuk-Kowerda, Dorota Dybowska, Anna Piekarska, Rafał Krygier, Beata Dobracka, Jerzy Jaroszewicz.

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CONFLICT OF INTEREST STATEMENT

Krystyna Dobrowolska has no conflict of interest to declare; Małgorzata Pawłowska has acted as a speaker for AbbVie and Gilead; Dorota Zarębska-Michaluk has acted as a speaker and advisor for AbbVie and Gilead; Piotr Rzymski has no conflict to declare; Ewa Janczewska has acted as a speaker and/or advisor for AbbVie, Gilead, MSD, Ipsen and has received funding for clinical trials from AbbVie, Allergan, Bristol Myers Squibb (BMS), Celgene, Cymabay, Dr Falk Pharma, Exelixis, GlaxoSmithKline (GSK) and MSD; Magdalena Tudrujek-Zdunek has no conflict of interest to declare; Hanna Berak has acted as a speaker for Abbvie; Włodzimierz Mazur has acted as a speaker and/or advisor for AbbVie, Gilead, Merck and has received funding for clinical trials from AbbVie, Gilead and Janssen; Jakub Klapaczyński has acted as a speaker for Gilead and AbbVie; Beata Lorenc has no conflict of interest to declare; Justyna Janocha-Litwin has no conflict of interest to declare; Anna Parfieniuk-Kowerda has no conflict of interest to declare; Dorota Dybowska has received funding for participation in the conference: from AbbVie; Anna Piekarska has acted as a speaker and/or advisor for AbbVie, Gilead, Merck and Roche; Rafał Krygier has acted as a consultant for AbbVie and Gilead; Beata Dobracka has no conflict of interest to declare; Jerzy Jaroszewicz has acted as a speaker and/or advisor for AbbVie, Gilead, Merck, Roche, Alfasigma, MSD, Gilead and PRO.MED; Robert Flisiak has acted as a speaker and/or advisor and has received funding for clinical research from AbbVie, Gilead, Merck and Roche.

ETHICS STATEMENT

This study was retrospective, non-interventional and based on data collected in the national EpiTer-2 database. Therefore it does not require approval of the Ethics Committee. Due to the retrospective nature of the presented study, written consent by participants was not necessary. The patients' data was protected according to the European Union General Data Protection Regulation.

INFORMED CONSENT STATEMENT

Due to the retrospective nature of the study, a waiver of consent was in effect.

DATA AVAILABILITY STATEMENT

Data supporting reported results can be provided upon request from the corresponding author.

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